REMARKS

Applicants gratefully acknowledge telephonic conversation with the Examiner on March 22, 2006.

Claims 36 - 51 are now pending in the application. Claims 7, 22 -25 stand withdrawn and claims 1-6, 8, 10- 21, 26 – 35 stand cancelled. The amendments are fully supported by the claims as filed and no new matter is believed to have been added.

The Examiner maintained her rejection of claims 13 – 14, 30 – 31 and 34- 35 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner maintained her rejection of claims 1-6, 13-15, 20-21, 27 – 29 and 33 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner maintained her rejection of claims 1-6, 13 – 15, 20 – 21 and 26 – 35 under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter.

The Examiner rejected claims 1-6, 13- 15, 20-21 and 26-35 under 35 U.S.C. § 112, first paragraph, as lacking in enablement.

The above amendments and the following remarks have addressed all the grounds for rejection and/or objection or have otherwise rendered them moot. Applicants respectfully request the Examiner reconsider all outstanding rejections, and that they be withdrawn.

Rejection under 35 U.S.C. § 112, First Paragraph

Written Description Rejection of Claims 13 – 14, 30 – 31 and 34- 35; claims 1-6, 13-15, 20-21, 27 – 29 and 33; and claims 1-6, 13 – 15, 20 – 21 and 26 – 35;

New Matter Rejection of Claims 1-6, 13 – 15, 20 – 21 and 26 – 35; and

Non-Enablement Rejection of claims 1-6, 13- 15, 20-21 and 26-35

The Examiner makes the following assertions:

1. The claims lack sufficient written description of a method for preparing a hybrid polypeptide comprising providing a polynucleotide encoding the plant hybrid polypeptide; an introduction step; a culturing step and a recovering step;

2. The claims encompass significantly more than just the timothy grass pollen allergens or even a specific allergen and are drawn to absolutely any plant allergens and any modifications or fragments thereof;

3. There is no disclosed correlation between function and structure of the sequence even if there is a method of obtaining the claimed sequence;

4. There is no description of the structure of the fragments of nucleic acids that must encode the hybrid polypeptide;

5. There is no method for preparing a hybrid polypeptide comprising fragments of polynucleotide;

6. Arguments about protective antibodies or epitope sites fail to address the description of such methods of (sic) fragments;

7. There is no disclosure of a method for preparing a hybrid polypeptide comprising fragments consisting of at least eight consecutive amino acids from the respective allergenic proteins;

8. The specification lack sufficient variety of species to reflect the variance in genus since the specification does not provide any examples of derivatives;

9. There are no in vivo experiments;

10. Applicants must provide sequence information as claimed in order for the Applicant's arguments, declarations and amendments to be persuasive;

11. There is no written description of a hybrid polypeptide comprising at least two different plant allergenic proteins or fragments thereof characterized in that said hybrid polypeptide has reduced allergenic activity compared with the allergenic protein from which it is derived and which in vivo induces protective antibody response;

12. The specification only describes recombinant timothy grass pollen allergens and there is no description of a hybrid polypeptide comprising any other type of plant allergen;

13. A hybrid polypeptide described only by a functional characteristic fails to meet the written description requirement;

14. There is no guidance as to what amino acids may or may not be included without causing a detrimental effect to the fragments thereof claimed and without specifically recited sequences, the skilled artisan cannot envision the detailed structure of the fragments thereof;

15. At best, applicants have shown that there were in possession of the entire sequence of timothy grass allergens, but have not shown that they were in possession of fragments capable of inducing an antibody response;

16. There is no disclosure of a highly conserved and immunogenic region in the plant allergen;

17. There is no teaching of a hybrid polypeptide comprising the generic components which induce an in vivo protective antibody response in any host;

18. There is no challenge experiments which would show that in vivo protection has been achieved;

19. The specification is not enabled for the induction of a protective immune response without a clear teaching of the immunoepitopes that induce a protective immune response; the specification lacks any description of a structure or relevant identifying characteristics;

20. There is no evidence that the instantly claimed hybrid polypeptides will have the ability in vivo to induce a protective antibody response;

21. The specification lacks a clear demonstration that the hybrid polypeptide of the instant claims is suitable for immunization;

22. The ability to reasonably predict the capacity of a single immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic; and without

this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed hybrid polypeptides.

Applicants respectfully disagree and now traverse as follows.

1. Applicants Respectfully Request the Examiner to be Pointed in her Rejections

Applicants' prior claim drafting scheme was presented with an eye to isolating matters for which there might exist genuine grounds of contention. Thus, claims were separately drawn to hybrids allergens comprising the wild-type allergens, to hybrids of modified wild-type allergens, and to hybrids of fragments of wild-type allergens. Applicants would be greatly aided in advance of this prosecution if the Examiner would be pointed so that Applicants can be more clearly informed of the Examiner's contentions should it still become necessary. Applicants would also greatly appreciate indication of particular phraseology or choice of words which the Examiner deems objectionable. Applicants would also greatly appreciate an affirmative indication of allowable subject matter.

It is the Examiner's primary contention that Applicants do not have in their possession, as at the filing date of this application, a universe of hybrid allergens and fragments thereof. In that regard, Applicants have re-drafted the claims, in part, to claim hybrids of timothy grass pollen allergens for immunotherapeutic applications which they undoubtedly had possession of at least. Applicants have also re-written the claims to recite the patentably distinct methodology of the present invention in a manner that obviates the Examiner's arguments as to the structure of the particular hybrid allergens.

In the sections that follow, Applicants will meet the Examiner's grounds for rejections under 35 U.S.C. § 112, first paragraph, by citation to specific textual references thereto. Applicants are in no way representing that the cited portions are the only portions of the specification on point and duly request the Examiner to consider the specification as a whole in deciding what Applicants had possession of as at the filing

date of the present invention. Further, Applicants are absolutely under no obligation, as a matter of law, to burden the instant Application with subject matter which is within easy and ready reach of one of skill in the art to which this invention pertains as at the time of filing the current Application.

2. Basic Principles of the Invention

> The inventors demonstrated that it is possible to generate by recombinant DNA technology, hybrid allergens which consist of immunologically unrelated allergens and their epitopes. Page 7, paragraph 3.

The Applicability of this concept was demonstrated using timothy grass pollen allergens.

> In a first step frequent co-sensitizations were determined using purified recombinant timothy grass pollen allergens to select the most frequently recognized allergen combinations for the hybrid allergen approach. According to the pilot experiments hybrids consisting of immunologically unrelated major timothy grass pollen allergens were engineered. Page 8, paragraph 1.

> The hybrid allergen approach will open new avenues for diagnosis and treatment of Type I allergy. Hybrids consisting of the most frequently recognized allergens with preserved epitopes represent candidate molecules for in vitro as well as in vivo allergy screening tests. Page 8, paragraph 2.

> Recombinant hybrid allergens can also be used for immunotherapy. They can either be composed of the biologically active components or of hypoallergenic allergen units. Hybrid allergens covering frequent co-sensitization patterns may then be used for the treatment of allergies to complex allergen sources, e.g., grass pollen allergy because they resemble the relevant epitopes of the complete extract. Since the hybrid allergens consist of defined components it will be possible to produce well defined formulations for vaccination treatment. Hybrid allergens produced out of hypoallergenic variants will be tolerated in high doses and thus can be used like vaccines regularly used for prevention of viral infections. In this respect it may be considered to use hybrid allergens containing the epitopes of the most relevant allergens for prophylactic vaccination or tolerance induction even in not yet sensitized individuals. Page 8, paragraph 3 – page 9, paragraph 1.

> The fact that the fusion of different antigenic components in form of a hybrid molecule increased the immunogenicity of the individual components has several implications for allergen-specific immunotherapy and for vaccination in general. Allergens or antigens against which immune responses are desired and which *per se* exhibit low immunogenicity can be fused to hybrids to increase their immunogenicity without using other carrier proteins or adjuvants. This principle will allow to induce high levels of protective antibody responses against allergens, allergen fragments, allergen epitopes or mimicks thereof. Using this principle it is also possible to increase the immune response towards antigens/epitopes derived from infectious agents, tumors or other components against which it is difficult to induce immune responses. Page 9, paragraph 2.

3. The is adequate written description of a method for preparing a hybrid fusion polypeptide comprising providing a polynucleotide encoding the plant hybrid polypeptide; an introduction step; a culturing step and a recovering step

Contrary to the Examiner's assertion, there is adequate written description of a method for preparing a hybrid polypeptide comprising providing a polynucleotide encoding the plant hybrid polypeptide; an introduction step; a culturing step and a recovering step as exemplified by the following citation.

> The protocol for the construction of recombinant hybrid allergens is illustrated in Figure 2. As exemplified for a hybrid consisting of rPhl p 5 linked to rPhl p 1, cDNAs coding for the components whose sequences are already known are amplified with suitable primer pairs (Figure 2: Phl p 5: w, x; Phl p 1: y, z) in order to create overlapping ends. In a subsequent second PCR reaction, a cDNA comprising both cDNAs is created with primers specific for the 5′ end of the first cDNA (Phl p 5: w) and the 3′ end of the second cDNA (Phl p 1: z) using both PCR products of the first reactions as templates. Using this technology Applicants produced recombinant hybrids consisting of a combination of Phl p 5/Phl p 1, rPhl p 2/rPhl p 6, rPhl p 6/rPhl p 2 and of all four allergens (N-terminus-rPhl p 6-rPhl p 2-rPhl p 5-rPhl p 1-C-terminus), the latter referred to as the "giant". Example 2, Page 15, paragraph 2.

Example 2 is followed by a detailed description of the construction of expression plasmids for rPhl p 5/rPhl p 1-, rPhl p 2/rPhl p 6-, rPhl p 6/rPhl p 2-, and rPhl p 6/rPhl p 2/rPhl p 5/rPhl p 1 hybrid proteins. See page 12, paragraph 4 et seq.

The detailed description of the culturing of expression plasmids was followed by Example 3 in which Applicants presented a detailed description of the expression and purification of hybrid allergens using E. coli as the host cell. See page 14, paragraph 2 et seq.

4. The claims encompass significantly more than just the timothy grass pollen allergens and are drawn to absolutely any plant allergens and any modifications or fragments thereof

The inventors were first to demonstrate that it is possible to generate by recombinant DNA technology, hybrid allergens which consist of immunologically unrelated allergens and their epitopes and which can contain relevant epitopes in a well defined ratio. The Examiner is urged to contrast that with natural allergen extracts which consist of a difficult to standardize mixture of allergens and non-allergenic materials.

Applicants disclosed that:

> In the broadest scope of the present invention any polypeptide may be used in the hybrid polypeptide which may be involved in vaccination. The polypeptide may be derived from viruses such as HI, HC-viruses, bacteria, tumor antigens or plant allergens. Page 2, paragraph 3.
>
> Allergen sources from which the allergenic proteins are derived may be major grass pollen, mite, bee venom or animal hair dander allergens. Specific examples of allergenic proteins are the group 1, group 2, group 4, group 5 group 6, group 11, group 12 and group 13 allergens of major grass pollen, Der p 1 and Der p 2 (mite), phospholipase from bee venom and Fel d 1 (cat). Page 2, paragraph 5.

Applicants used timothy grass pollen allergens as their preferred embodiment to demonstrate the validity of their invention. One of skill in the art understands that the principle set forth in the Application will apply to a wide variety of hybrid allergens.

Contrary to the Examiner's assertion above, Applicants are not claiming an arbitrary universe of hybrid allergens. Rather, Applicants have expressly delimited as hybrid allergens of interest, those that induce IgE-blocking antibodies in vivo and in turn

have reduced allergenicity compared to the wild-type allergens from which they were derived.

Moreover, one of skilled in the art knows how to generate protein or cDNA fragments, and armed with the teachings of this invention, such a skilled artisan knows how to generate fusion proteins of those fragments and can use a suitable immunological model to test whether such hybrid induces IgE-blocking antibodies and have reduced allergenicity compared to the wild-type allergens.

In order to advance the prosecution of the current application, Applicants have amended the claims to recite hybrid allergens comprising fusion proteins of timothy grass pollen allergens. Using the experimental protocol of Example 2, page 12, and as clearly shown in Figure 2, Applicants had in their possession, as at filing date, a fusion protein of timothy grass pollen allergens whose sequences were already known as made clear in the prior filed Rule 132 declaration.

In other cases, Applicants have re-drafted their claim to seek patent protection for their methodology comprising the steps of:

(a) providing hybrid of naturally occurring plant allergens;

(b) challenging an immunological model with said hybrid allergen;

(c) selecting as candidate immunotherapeutic agents, those hybrid allergens which induce IgE-blocking antibodies and have reduced allergenic activity compared with the respective wild-type allergens.

Clearly, the exact molecular structure of the hybrid allergens is not an element of the claims exemplified by the above methodology and arguments as to disclosure of the primary sequence of the hybrid allergens have been rendered moot.

5. The Examiner's insistence on a disclosed correlation between function and structure of the sequences of the hybrid allergen or that Applicants must provide

sequence information as claimed in order for the Applicant's arguments, declarations and amendments to be persuasive is in error.

The Examiner's insistence that there is no disclosed correlation between function and structure of the sequence of the hybrid allergens even if there is a method of obtaining the claimed sequence and that Applicants must provide sequence information as claimed in order for the Applicant's arguments, declarations and amendments to be persuasive is clearly erroneous for the following reasons.

Prior to the instant invention, there were ordinarily two ways of sensitizing patients against IgE-mediated hypersensitivity reactions. One way is to isolate wild-type allergens, sequence them, undertake detailed study of the primary, secondary and tertiary structures of the proteins, carry out antibody-binding studies for epitopic mapping of the wild-type allergen, then having identified key epitopic sites, proceed to rationally modify the primary structure of the allergens in order to hypoallergenize them and use those hypoallergenic derivates as immunotherapeutic agents. A patent claiming the hypoallergenic derivative of the wild-type allergen in this case must necessarily disclose the structure of the hypoallergenic protein.

The other way of sensitizing patients against IgE-mediated hypersensitivity reactions is to challenge the patient with crude extracts of wild-type allergens. A disclosure directed to claims of said crude extract of wild-type allergens is enabling if the disclosure teaches how to make and use the crude extract without requiring that the inventor disclose the primary structures of all the proteins that comprise the crude extract.

The current invention is a more rational way of rapidly identifying immunotherapeutic agents without the need for experimentally intensive protein chemistry and yet develop allergens of known composition capable of sensitizing patients against a broad spectrum of allergens. This is accomplished by making hybrid allergens of known wild-type allergens, challenging an immunological model with said hybrid

allergens, identifying those hybrid allergens that induce IgE-blocking antibodies and are hypoallergenic compared to wild type allergens. This methodology includes using hybrids of fragments and modifications of wild-type allergens, said fragments and modifications to be generated by methods all too well known to skilled artisans in the art.

Thus, when the Examiner asserts that there is no disclosure of a highly conserved and immunogenic region in the plant allergen, the Examiner is thinking in terms of the experimentally intensive methodology of immunotherapeutic agent design involving extensive protein characterization and that is precisely what the current invention seeks to avoid. Many allergens have been identified and sequenced. There is no requirement under the law that Applicants burden their specification with already known and disclosed sequences in order to perfect an entitlement to a fusion protein of those sequences to be used as immunotherapeutic agents. Prior to the current invention, no one has demonstrated that fusion proteins of known allergens can be used in allergy immunotherapy. Applicants have demonstrated, using the case of timothy grass allergens that said fusion proteins can be used for allergy immunotherapy. Applicants believe that their disclosure in enabling for the structure of fusion proteins of all known allergens, to be used as immunotherapeutic agents, as at the time of filing the present invention.

Nevertheless, in order to advance the prosecution of this application and secure patent rights to the invention, the claims have been re-drafted to claim the above methodology and to claim hybrid allergens of timothy grass pollen allergens.

Further, the Examiner asserts that there is no disclosure of a highly conserved and immunogenic region in the plant allergen. It should be clear at this point that this invention does not concern itself with epitopic characterization of any particular plant allergen. Even then, Applicants were able to validate the immunochemistry of their hybrid allergens by teachings such as the following except regarding the repertoire of the T-cell and B cell epitopes of the hybrid proteins.

> Recombinant hybrid allergens contained the complete primary amino acid sequences of their components and thus the complete repertoire of T cell epitopes of the single allergens. The presence of B cell epitopes was investigated with antibodies of predefined specificity for the individual components and by immunological competition experiments. Figure 4 shows that the "giant" is recognized by antisera raised against rPh l p 1, rPhl p 2, rPhl p 5 and rPhl p 6, respectively (Figure 4, row A: 1-4). The correct expression of the C-terminal hexahistidine tag was demonstrated by the reactivity of a mouse monoclonal anti-Histag antibody which specifically recognized the "Giant (Figure 4: row A, 5) but not rPhl p 2 containing no hexahistidine tag (Figure 4: row B, 5). Recombinant Phl p 2 (row B: 1, 3, 4) and rPhl p 5 (row B: 2) (negative controls) did not react with the antisera (Figure 4: row B) Page 15, paragraph 3.

6. There is adequate teaching of the structure of the fragments of nucleic acids that must encode the hybrid polypeptides and there is sufficient disclosure of method for preparing a hybrid polypeptide comprising fragments or modifications thereof of polynucleotides.

The Examiner asserts that there is no description of the structure of the fragments of nucleic acids that must encode the hybrid polypeptides. The Examiner is again in error.

Example 2 on page 12 shows how to construct recombinant hybrid allergens. Said method was also clearly illustrated in Figure 2 which clearly shows the construction of fusion nucleotides for subsequent insertion into a suitable expression vector.

On page 12, paragraph 3 up to page 14, paragraph one, Applicants presented a detailed disclosure of how to construct plasmids of hybrid proteins of timothy grass pollen allergens after first obtaining the cDNAs of such hybrids.

The methods disclosed presume that the protein and nucleotide sequence of the wild-type allergens comprising the hybrid allergens are already known; which in fact they are. The disclosure also presumes that one of skill in the art has more than ample guidance based on the state of the art, as at the time of filing the current application, of how to generate fragments of nucleic acids. Having taught how to generate recombinant

hybrid allergens and how to generate cDNAs of said recombinant hybrid allergens, one of skill in the art is already amply informed about how to generate fragments of nucleic acids of wild type allergens and using the disclosed method, generate hybrid allergens of said fragments of wild-type allergen.

Applicants further presented guidance on the structure of said fragments by teaching that they be at least eight consecutive amino acids of the wild-type allergen.

As for the Examiner's insistence that Applicants must not only disclose the structure of the fragments, but must also teach which eight consecutive amino acids, Applicants believe that the Examiner's insistence is not consonant with what Applicants have discovered and are claiming.

Applicants are claiming hybrid allergens comprising fusion protein of fragments of wild type allergens, for use as immunotherapeutic agents, said hybrid allergens selected by a process of first using them to challenge an immunological model, then assaying the blood of the model for elicitation of IgE-blocking antibodies and IgE.

Applicants have amended their claims to relate to this methodology and also to claim hybrids of timothy grass pollen allergens, including fragments thereof, and believe that the claims are adequately enabled and allowable. Further, the Examiner's assertion that the specification lack sufficient variety of species to reflect the variance in genus since the specification does not provide any examples of derivatives is obviated by the foregoing remarks. Further, the Examiner's assertion that there is no guidance as to what amino acids may or may not be included without causing a detrimental effect to the fragments thereof claimed and further that without specifically recited sequences, the skilled artisan cannot envision the detailed structure of the fragments thereof are also obviated by the foregoing remarks.

Regarding modifications of wild-type allergens or modifications of fragments of wild-type allergens, the specification teaches that:

> The term "allergenic proteins or fragments thereof" comprises also modifications of the allergens wherein the sequence of the naturally occurring allergen has been slightly modified by substitutions of single amino acids or nucleotides whereby the allergenic potential has been substantially maintained. Page 2, paragraph 4.

Based purely on state of the art as at the time of filing this application, one of skill in the art, giving a polynucleotide or polypeptide sequence of plant allergens can make modifications of said polynucleotide without requiring any teaching from the description of how to do so. The invention however teaches that a fusion protein of fragments or modifications of fragments of the wild-type allergen can be screened as immunotherapeutic agents by using them to challenge a suitable model and selecting as candidates those that induce IgE-blocking antibodies and are hypoallergenic compared to wild-type allergens.

7. The Specification is replete with *in vivo* experiments and the Examiner's assertion that there is no challenge experiments which would show that in vivo protection has been achieved or that there is no teaching of a hybrid polypeptide comprising the generic components which induce an in vivo protective antibody response in any host is clearly erroneous.

The Examiner asserts that there are no *in vivo* experiments and no demonstration of protective antibody response in any host is clearly erroneous. On the contrary, the specification is replete with *in vivo* experiments as shown by the following excerpts.

> To evaluate whether immunization with the hybrid allergens induces IgG antibodies that recognize the individual allergen components, groups of 8 mice each were immunized with the hybrids, the individual allergens or timothy grass pollen extract. Figure 5 demonstrates that the average IgG_1 responses induced by the hybrid molecules to each of the individual allergens (rPhl p 1, rPhl p 2, rPhl p 5, or rPhl p 6) were higher than those obtained by immunization with the single allergen components. High IgG_1 antibody levels induced by the hybrids were already detectable 4 weeks after the first immunization and had increased further after 4 more weeks. Perhaps most interesting was the finding that the hybrid molecules

induced higher IgG_1 levels to the individual allergen components than timothy grass pollen extract (Figure 5). The latter was particularly evident for Phl p 2, Phl p 6 and Phl p 1 which were poorly recognized by extract-induced antibodies, whereas the hybrid molecules induced vigorous anti-Phl p 1-, anti-Phl p 2- and anti-Phl p 6 antibody responses (Figure 5). Page 17, paragraph 1.

Likewise we found that immunization with the giant molecule induced stronger antibody responses to each of the components (Phl p 1, Phl p 2, Phl p 5, Phl p 6) than immunization with the individual antigens (Figure 6A) or an equimolar mixture of the antigens (Figure 6B). Immunization with the giant yielded also better immune responses than immunization with timothy grass pollen extract. IgG antibodies induced with timothy grass pollen extract exhibited lower reactivity to the giant and to the extract than those induced with the giant (Figure 7A, B). Page 17, paragraph 2.

Groups of 8 female BALB/c mice (age: 8 weeks) (Charles River, Germany) were immunized subcutaneously with rPhl p 1, rPhl p 2, rPhl p 5, rPhl p 6, rP2-P6, rP6-P2, rP5-P1, the giant molecule, timothy grass pollen extract, or an equimolar mixture of rPhl p 1, rPhl p 2, rPhl p 5, and rPhl p 6 adsorbed to $Al(OH)_3$ (Alu-Gel-S, Serva, Ingelheim, Germany). Animals were maintained in the animal care unit of the Institute of Pathophysiology, University of Vienna, according to the local guidelines for animal care. Mice were immunized and bled from the tail veins in four-week intervals and sera were stored at -20°C until analysis. Page 17, paragraph 3.

Regarding challenge experiments which would show that *in vivo* protection has been achieved, the specification specifically teaches that:

Next we examined whether mouse antibodies induced with the hybrid molecules can block the binding of grass pollen allergic patients IgE antibodies to purified grass pollen allergens (Table 3). ELISA competition experiments performed with sera from 4 representative grass pollen allergic patients showed that antibodies induced by the hybrid molecules strongly inhibited IgE binding to the purified allergens: IgG antibodies induced with the rP2-P6 and the rP6-P2 hybrid molecule caused a 48%-54% inhibition of IgE binding to Phl p 2 and a 54%-67% inhibition of IgE binding to Phl p 6 (Table 3A). By contrast, the inhibition of IgE reactivity yielded by preincubation with antibodies induced with rPhl p 2 and rPhl p 6 alone was very low (0-15%) (Table 3A). Anti-P5-P1 antibodies caused a more than double inhibition of IgE binding to Phl p 5 (59.5% average inhibition) than antibodies raised against Phl p 5 alone (28%) (Table 3B).

> The inhibition of IgE binding to Phl p 1 yielded with the antibodies raised against the rP5-P1 hybrid (18.5% average inhibition) and Phl p 1 alone (29.5% average inhibition) were lower (Table 3B). Page 18, paragraph 3.

It should be pointed out that the terms "protective antibodies", "blocking antibodies" refer to IgE-blocking antibodies as properly understood by one of skill in the art and as exemplified by the following excerpt:

> Similar results were obtained with the giant molecule which induced IgG antibodies that efficiently blocked the binding of grass pollen allergic patients IgE to Phl p 1, Phl p 2, Phl p 5, Phl p 6 and timothy grass pollen extract (data not shown). Page 18, paragraph 4.

To more clearly and distinctly claim the invention, Applicants have amended the claims to refer to treatment of IgE-mediated hypersensitivity reaction, said treatment attained by virtue of induction of IgE-blocking antibodies by hybrid allergens. The foregoing has also obviated the Examiner's argument that the specification lacks a clear demonstration that the hybrid polypeptide of the instant claims is suitable for immunization.

The Examiner asserts that the ability to reasonably predict the capacity of a single immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic; and without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed hybrid polypeptides. The Examiner further asserts that there is no evidence that the instantly claimed hybrid polypeptides will have the ability *in vivo* to induce a protective antibody response. The foregoing *in-vivo* experiments disclosed in the Application show that the Examiner's assertion regarding lack of *in vivo* validation of the claims of the instant invention is without basis.

Further, the Examiner's assertion that the specification is not enabled for the induction of a protective immune response without a clear teaching of the immunoepitopes that induce a protective immune response and that the specification lacks any description of a structure or relevant identifying characteristics is also without

basis. These issues have already been dealt with and the Applicants respectfully ask the Examiner to depart from the mindset that rigorous epitopic mapping of putative immunotherapeutic agents is the only means to rationally identify candidate agents. The current invention teaches an alternate methodology that is much less experimentally cumbersome.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office action and, as such, the present application is in condition for allowance. Applicants wish to expedite the prosecution process and if the Examiner believes, for any reason that personal communication will help expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Response is respectfully requested.

Respectfully submitted,

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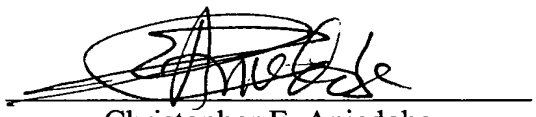

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